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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/501,787	02/11/2000	Laurent Coen	03495.0187	4369

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/22/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/501,787	COEN ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-11,31 and 33-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-11,31 and 33-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/12/2006 has been entered.

Claims 1-5, 8-11, 31, 33-46 are pending. Further, claims 8-11, 31, 33-46 are being examined to the extent that they read on SMN protein, as set forth previously.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 31, 34, 36, 37 and new claims 38-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5780024 in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990.

U.S. Patent No: 5780024 discloses an in vivo method for delivery (e.g. intramuscular, see col 4) of a composition (SOD:Tet451), comprising a the tetanus toxin C fragment recombinantly fused to a second protein (e.g. SOD-1, see the Abstract), wherein said second protein is fused downstream to the tetanus toxin C fragment (see col 6) and wherein the fusion protein is capable

of in vivo retrograde axonal transport and transynaptic transport in to the CNS (e.g. from systemic administration to the brain stem, see col 1). Further, U.S. Patent No: 5780024 disclosed that the method can be used in the treatment of neurodegenerative diseases of the CNS (see col 1 for example).

U.S. Patent No: 5780024 discloses that the tetanus toxin C fragment used in the method of delivery can include additional amino acids, see col 6, as a matter of routine optimization of operating perimeters; yet U.S. Patent No: 5780024 does not disclose, specifically, that the C-fragment should contain at least 11 amino acids of the B-fragment nor that the there should be exactly 11 (claim 37). U.S. Patent No: 5780024 disclose embodiments having 2 or 8 additional amino acids (col 6) and indicate that more or less are encompassed by the invention, and can be added, particularly as a matter of convenience in the cloning process, e.g. col 6, lines 37-40. However, Halpern et al. disclose the recombinant use of the tetanus toxin C-fragment including at least 9 amino acids of the B-fragment (second paragraph of the DISCUSSION on page 1007), and specifically teach that its probable that it is the addition of these amino acids of the B-fragment that results in the improved neuronal binding properties of the C-fragment, see page 1007, col 2, paragraph. Furthermore, Halpern teach that the addition a much greater portion of the B-fragment (e.g. 121 amino acids) might cause the undesirable property of insolubility, see page 1007, Col 2, 3rd paragraph. However Halpern also teach that a small number of amino acids, in addition to the nine residues of the B-fragment, may also aid in the improvement of the binding properties, e.g. the fragment used by Halpern contains and an additional 8 residues encoded by the vector, see second paragraph of the DISCUSSION on page 1007. Thus, the skilled would have looked to optimize the size of the additional B-fragment sequences as

differing not much than the nine residues taught by Halpern but perhaps as much as 17 residues. Therefore, at the time the instant invention was made, it would have been an obvious matter of routine optimization of operating parameters to use nine, ten, eleven, etc. additional amino acids of the B-fragment (as taught by Halpern) when practicing the invention disclosed in U.S. Patent No: 5780024 The motivation to do so was provided by both U.S. Patent No: 5780024, wherein it was taught that additional amino acids of the B-fragment may be added to the C-fragment as a matter of routine optimization, and Halpern et al. who teach that additional amino acids of the B-fragment may enhance the binding of the C-fragment to neuronal membranes, such activity being obviously important in the practice of the invention of U.S. Patent No: 5780024, e.g. see col 1, lines 64-col 2 line 9 of U.S. Patent No: 5780024 .

Applicant's arguments essentially evolve from two assertions: 1) that the basis of the rejection is an "obvious to try" standard, and 2) that one of ordinary skill in the art would not expect the fusion protein to undergo transynaptic transport. These arguments has been fully considered but not deemed persuasive.

The basis of the rejection is a simple routine optimization of operating parameters as specifically suggested by Halpern. who specifically teach that additional amino acids of the B-fragment may enhance the binding of the C-fragment to neuronal membranes, as discussed above. This is a specific teaching and not a situation where the "prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" as Applicant asserts.

Second, Applicant argues that the Office has not explained the basis for the asserted expectation that the fusion protein would be capable of transynaptic transport. This argument

has been fully considered but not deemed persuasive. The examiner has repeatedly pointed to col 4, lines 34-44 of the '024 patent, wherein it is specifically taught that the fusion peptide is expected to undergo "transynaptic transfer between neurons".

Claims 8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5780024 in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990, as applied to 1-8 , above, and in further view of U.S. Patent No: 6159948.

Applicant's elected species of SMN (claim 8) is not taught by either U.S. Patent No: 5780024 or Halpern et al, as discussed above, however U.S. Patent No: 6159948 teaches the treatment of neurodegenerative disorders (e.g. spinal muscular atrophy, col 1) comprising the administration of the SMN protein (a.k.a NAIP) wherein the SMN protein is a fused to tetanus toxin or a fragment thereof (see col 21, last paragraph). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, with reasonable expectation of success to modify the C-fragment of tetanus toxin as taught by Halpern and by U.S. Patent No: 5780024, as discussed above, with the SMN protein as taught by U.S. Patent No: 6159948, for use in a method to deliver the SMN protein to the central nervous system. The motivation to do so was provided by U.S. Patent No: 6159948 wherein it is stated that increased levels of SMN protein (NAIP) can provide neuroprotection against neurodegenerative diseases (see the Abstract, and col 1), wherein the SMN protein should be fused to tetanus toxin or a fragment thereof (see col 21, last paragraph).

On page 9 of the response, Applicant argues that the 6159948 does not disclose using at least 11 amino acids of fragment B. This argument has been fully considered but not deemed

persuasive. The addition of the fragment B amino acids is discussed above regarding U.S. Patent No: 5780024 and Halpern et al.

Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5780024 in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990 and U.S. Patent No: 6159948, as applied to claims 8 and 11, above, and in further view of Fishman et al., J. Neurological Sciences 98(311-325)1990.

Claims 9 and 10 require a method as claimed in claim 8 as discussed above, yet claims 9 and 10 also require that the composition comprise at least two of said second molecules (claim 9) or that the said second molecule be located upstream of the tetanus toxin fragment (claim 10). Fishman et al. teach that a second biologically active molecule can be conjugated to the tetanus C-fragment multiple times throughout the length (upstream or downstream) of the C-fragment (see page 313, middle paragraph and Figure 1, lanes 2 and 3). Therefore, it would be an obvious matter of routine optimization of operation parameters to incorporate at least two biologically active molecules to the C-fragment of the tetanus toxin, wherein at least one was associated upstream of the C-fragment, as taught by Fishman et al. when practicing the method of U.S. Patent No: 5780024 with the motivation to add amino acids of the B-fragment as taught by Halpern et al., as discussed above. The motivation to do so is provided by Fishman et al. who teach that multimeric complexes are desirable (page 13 middle paragraph). Fishman et al., also provide the artisan with a reasonable expectation of success because Fishman et al. teach that the large size of such complexes does not interfere with the uptake of the complexes into neurons (page 322, middle paragraph).

Applicant's arguments (page 8) have been addressed above regarding U.S. Patent No: 5780024 and Halpern and the addition of additional amino acids of the B fragment.

Claims 1-5, 31, 34, 36 and new claims 38-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. J. Biol. Chem. 270(25)15434-15442, 1995, in view of Halpern et al., Infection and Immunity,.58(4)1004-1009, April 1990.

Francis et al. disclose an in vitro method for delivery of a composition (SOD:Tet451), comprising a tetanus toxin C fragment recombinantly fused to a second protein (e.g. SOD-1, see the Abstract), wherein said second protein is fused downstream to the tetanus toxin C fragment (see col 6) and wherein, absent evidence to the contrary, the fusion protein is capable of in vivo retrograde axonal transport and transynaptic transport in to the CNS (e.g. from systemic administration to the brain stem, see page 15434). Francis et al. did not use the method for *in vivo* delivery, however they proposed to do so (see the Abstract, for example). Further, Francis et al disclosed that the method could be used in the treatment of neurodegenerative diseases of the CNS (15434 see col 1 for example). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made to with reasonable expectation of success to use the in vitro method of delivery disclosed by Francis et al. for in vivo delivery, as required by the instant claims. The motivation to do so was provided by Francis et al. who state the tetanus toxin has a well documented capacity for neuronal binding and internalization. In particular when administered systemically or intramuscularly to animals, the toxin is taken up selectively by motor neurons in the brain stem and spinal chord. The C-fragment retains these properties without the toxic domain (see 15434 see col 1). Further, Francis et al. hypothesize

that their disclosed fusion protein could increase the delivery of the SOD-1 protein to the central nervous system in general and motor neurons in particular, potentially providing effective enzyme therapy to neurons (see 15434 see col 1).

Francis et al. disclose that it is the C-fragment of tetanus that provides for neuronal binding and internalization without toxicity, yet Francis et al. do not disclose, specifically that the C-fragment should contain at least 11 amino acids of the B-fragment. Halpern et al. disclose the recombinant use of the tetanus toxin C-fragment including at least 9 amino acids of the B-fragment (second paragraph of the DISCUSSION on page 1007), and specifically teach that its probable that it is the addition of these amino acids of the B-fragment that results in the improved neuronal binding properties of the C-fragment, see page 1007, col 2, paragraph. Furthermore, Halpern teach that the addition a much greater portion of the B-fragment (e.g. 121 amino acids) might cause the undesirable property of insolubility, see page 1007, Col 2, 3rd paragraph. However Halpern also teach that a small number of amino acids, in addition to the nine residues of the B-fragment, may also aid in the improvement of the binding properties, e.g. the fragment used by Halpern contains and an additional 8 residues encoded by the vector, see second paragraph of the DISCUSSION on page 1007. Thus, the skilled would have looked to optimize the size of the additional B-fragment sequences as differing not much than the nine residues taught by Halpern but perhaps as much as 17 residues. Therefore, at the time the instant invention was made, it would have been an obvious matter of routine optimization of operating parameters to use nine, ten, eleven, etc. additional amino acids of the B-fragment (as taught by Halpern) when practicing the method taught and proposed by Francis et al. The motivation to do so was provided by Halpern et al. who teach that additional amino acids of the B-fragment may

enhance the binding of the C-fragment to neuronal membranes, such activity being obviously important in the practice of the method taught and suggested by Francis et al.

Applicant's arguments regarding Halpern have been essentially addressed above. Applicant further argues that neither Halpern or Francis et al. disclose in vivo transynaptic transport and that one would be surprised to obtain the effects Applicants have discovered. This argument has been fully considered but not deemed persuasive. Referring to the uptake of the fusion protein by motor neurons, at page 15441, col 1, last sentence of the first full paragraph, Frances et al. teach that through this pathway, the hybrid protein could access other central nervous system neurons as well, given the ability of TTC to undergo retrograde trans-synaptic transfer". Thus, Frances et al. specifically assert that hybrid protein is capable of transynaptic transport. Applicant has provided no reasons as to why one of ordinary skill in the art would not believe the teachings of Frances et al.

Claims 31, 33-36 and new claims 38-46 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. J. Biol. Chem. 270(25)15434-15442, 1995 in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990, as applied to claim 8, above, and in further view of U.S. Patent No: 6159948.

Applicant's elected species of SMN (claim 8) is not taught by either Francis et al. or Halpern et al, as discussed above, however U.S. Patent No: 6159948 teaches the treatment of neurodegenerative disorders (e.g. spinal muscular atrophy, col 1) comprising the administration of the SMN protein (a.k.a NAIP) wherein the SMN protein is a fused to tetanus toxin or a fragment thereof (see col 21, last paragraph). Therefore, it would have been obvious to one of

ordinary skill in the art, at the time the invention was made, with reasonable expectation of success to modify the C-fragment of tetanus toxin as taught by Halpern et al. and by Francis et al., as discussed above, with the SMN protein as taught by U.S. Patent No: 6159948, for use in a method to deliver the SMN protein to the central nervous system. The motivation to do so was provided by U.S. Patent No: 6159948 wherein it is stated that increased levels of SMN protein (NAIP) can provide neuroprotection against neurodegenerative diseases (see the Abstract, and col 1), wherein the SMN protein should be fused to tetanus toxin or a fragment thereof (see col 21, last paragraph).

Applicant's arguments regarding Halpern et al., and Francis et al. have been addressed above.

New Rejection:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10, 11, 43 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims require that the protein be "upstream" (claim 10) or "downstream" (claim 11) or that the toxin be "downstream" (claims 43 and 44). The use of the terms "upstream" and "downstream" is ambiguous in the art and could be taken to mean a position in a signal transduction pathway, in a fusion protein, or in a transport pathway, etc. The specification does not define the intended meaning; thus an artisan could not be reasonably sure of the metes and bounds of the claim.

Conclusion

No claims are allowable

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867. Official papers filed by fax should be directed to **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

December 16, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER